Intraoperative Radiotherapy (IORT) for Locally Advanced Colorectal Cancer

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Colorectal cancer is the second most frequent malignant tumor in the United States and fourth most frequent tumor in Korea. Surgery has been used as a primary treatment modality but reported overall survivals after curative resection were from 20% to 50%. Local recurrence is the most common failure in the treatment of locally advanced colorectal cancer. Once recurrence has developed, surgery has rarely the role and the five year survival of locally advanced rectal cancer is less than 5%, in spite of massive combination therapy.

Intraoperative radiotherapy (IORT) with or without external beam irradiation has been advocated for reducing local recurrence and improving survival. The recent report of local failure by this modality was only 5%, this indicated that significant improvement of local control could be achieved.

We performed 6 cases of IORT for locally advanced colorectal cancer which is the first experience in Korea. Patient's eligibility, treatment applicator, electron energy, dose distribution on the surface and depth within the treatment field and detailed skills are discussed. We hope that our IORT protocol can reduce local failure and increase the long term survival significantly.

Key Words: Intraoperative radiotherapy (IORT), Locally advanced colorectal cancer, Local control.

INTRODUCTION

Colorectal cancer is the second most frequent cancer in the United States[1] and fouth most frequent malignant tumor in Korea[2]. Slurgery has been used as a primary treatment modality, but reported overall survival after curative resection were 20%[3]~57%[4], depends on the extent of disease and institutions.

This figure has not changed over the last decades, inspite of progressive improvement in surgical skills and supportive therapy.

Local recurrence is the most common failure in the treatment of rectal cancer. Once pelvic recurrence has developed, surgery is rarely possible and five year survival is less than 5%[4~6]. Many efforts with combination modalities, including surgery, radiotherapy, chemotherapy[7,8] and immunotherapy[6] have been directed to reduce local failure, but still reported local failure is 40~70%[9]. Therefore, reduction of the local failure is the important key which improve local control and survival.

Intraoperative radiotherapy (IORT) with or without external irradiation have been advocated for reducing local failure and improving survival[10~16]. Recently reported local failure in locally advanced rectal cancer by this modality was only 5%[12], this indicated that the significant improvement of local control could be achieved by IORT with or without external beam irradiation.

We performed 6 cases of IORT for locally advanced colorectal cancer which is the first experience in Korea. Patient's eligibility, treatment cone, electron energy, dose distribution on the surface and depth within the field and detailed skills are discussed. We hope that our experience could be encouraging other institutions which are preparing for IORT.

MATERIALS AND METHODS

On May 30th, 1991, we performed the first case of locally advanced rectal cancer which is the first experience of IORT for rectal cancer in Korea. Details of our prospective protocol was described in Table 1. So far, we performed 6 cases of IORT for locally advanced colorectal cancers by our protocol (Table 2).

1. Patient's Eligibility

The eligible criterias for our protocol are 1)

primary or recurrent, locally advanced colorectal cancer patients, 2) location of tumor should be adequately adjustable for IORT applicator anatomically, 3) No evidence of distant metastasis. The definition of locally advanced cancer in our protocol means clinical tumor fixation or adhesion with no evidence of metastasis in preoperative evaluation by means of barium enema and abdominopelvic CT.

2. Operation and IORT Procedure

All procedures were performed in our Linac room from start to the end, which is the most ideal condition[15,16], because moving an uncoscious patients attached to an anesthesia machine from operation room to the radiation treatment rooms is cumbersome for not only surgeon but also all participating personels and patients in our program. Surgical incision should be a little more generous than those routine operation to achieve adequate mobilization and exposure for IORT. The type of surgery such as abdominoperineal resection or low anterior resection, was decided by surgeon, depend on the location and the extent of disease. Complete resection is the aim of the surgery but microscopic or gross residual cancer could not avoided and this is the main target of IORT.

After resection of the tumor, surgeon and radiotherapist discussed about target area, cone size, inclination of beveled cone, shielding area and abdominal or perineal approach of IORT. Ureter should be excluded from the field of IORT unless gross tumor infiltration is evident. Expected anastomosis stumps should be excluded or shielded for avoiding unwanted leakage problems. Treatment applicator should be cheked for appropriate position and completely excluding of radiosensitive organs from the field.

During irradiation, patient's condition and anesthesia equipments are monitored outside of treatment room. After irradiation, field of IORT is marked with surgical clips which is helpful for planning of external beam irradiation. Reconstruction may be completed as a conventional operation procedure. Peritoneal reconstruction of the pelvic floor was performed with proper sized mesh for minimizing small bowel injury by upward displacement of small bowels during external irradiation.

Mean delayed time for IORT, compared to conventional operation is approximately 30 minutes, including preperation, treatment and removing of applicator.

Table 1. Treatment Protocol

For primary locally advanced cancer :		
	Resection	RT + Chemotherapy
		RT
For recurrent, locally advanced cancer :		
	Resection	RT + Chemotherapy
		RT

* RT : IORT + Pre- or Post-operative irradiation
IORT : Single 1200cGy with 9 MeV electron at 90% isodose line.
Pre-, or Postoperative irradiation ; 4500cGy for full pelvis.
Chemotherapy ; 5—FU + Leucovorin

Table 2. Patients Characteristics

Case	Sex/Age	Stage	Location	Operation	IORT		
					Appl. size	Energy (MeV)	Dose (cGy)
1.	61/F	C—3	Rectum	Mile's op.	6cm	9	1200
2.	74/M	B—3	Rectum	Low-anterior	6cm	9	1200
3.	31/M	B—3	Rt. colon	Hemicolectomy	8cm	9	1200
4.	65/F	B—3	Rectum	Low-anterior	6cm	9	1200
5.	56/F	C—3	Rectum	Mile's op.	7cm	9	1200
6.	50/F	C—3	Rectum	Mile's op.	7cm	9	1200

* Stage ; Modified Astler—Coller, Dukes staging system for colorectal cancer.
("In" Cancer Treatment. 3rd ed., Mose. 1989, pp389)
B—3 : Tumor adherent to or invading adjacent structures ; node negative.
C—3 : Tumor adherent to or invading adjacent structures ; node positive.

3. IORT Applicator

Various shapes and sizes of applicator were designed for different tumor size and locations. Square, circular, elliptical shape with bevels of 0°, 15° and 30° inclination were fabricated for adjusting to the slopped surface of treatment area (Fig. 1).

Various internal diameter of each shape of applicator ranging from 5 cm to 10 cm were made of 0.6 cm thickness of acryl which is possible to observe the inside of the field without periscope. All participating members can see the treatment area directly through the transparent acryl which is very handy and time saving. 1.3 mm thickness of acryl cover was added on the tip of the applicator for

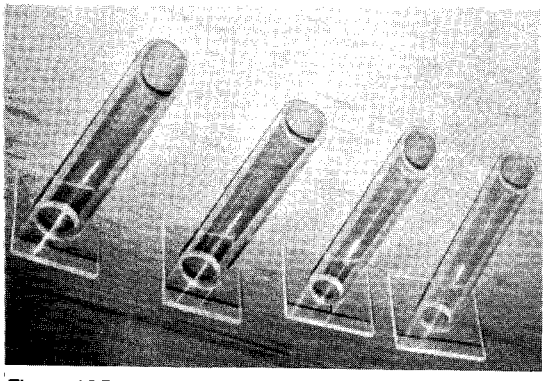

Fig. 1. IORT applicators. Various sized, 0°, 15°, 30° beveled, eliptical and circular applicators.

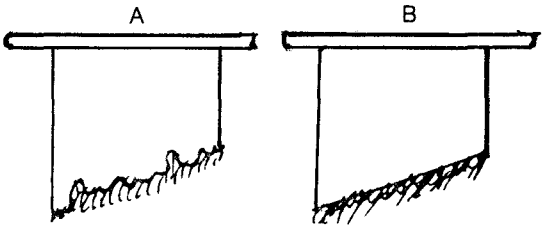

Fig. 2. A). Applicator without acryl cover. Note irregular surface which may cause inhomogenous dose distribution.
B). Applicator with acryl cover.

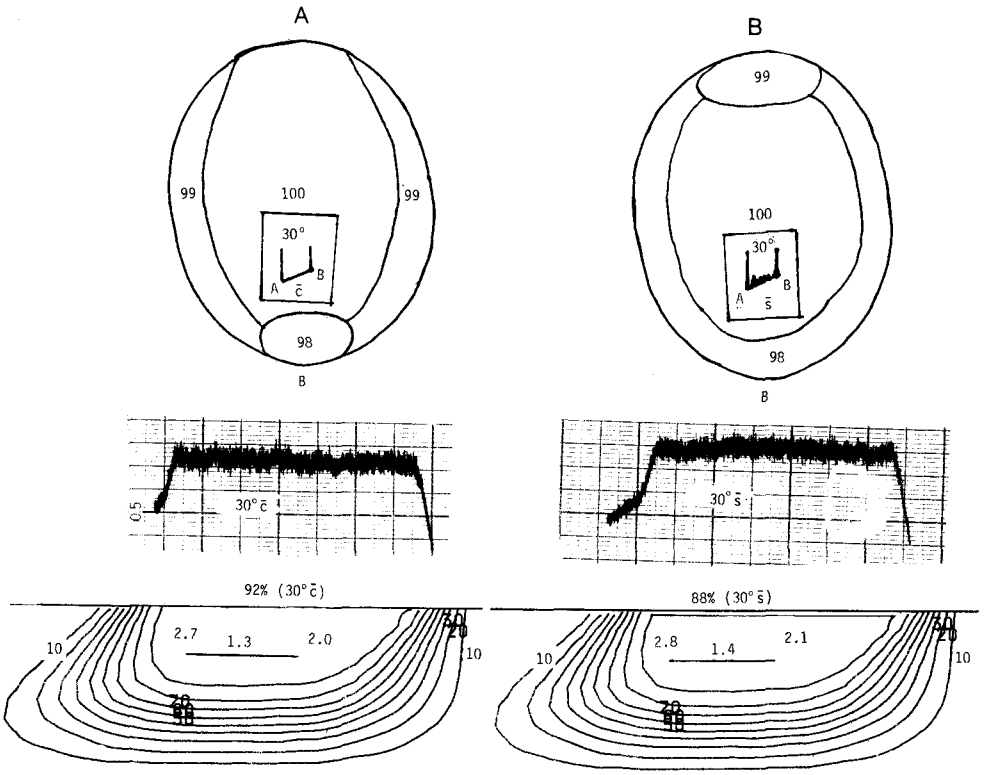

Fig. 3. Surface and depth dose distribution of the 7 cm diametered circular applicator with (I) without (II) acryl cover. Note better surface dose distribution.

flattening of target surface which is helpful for homogenous dose distribution (Fig. 2).

Approximately 2% of leakage was measured at just outside of applicator. 2 mm of lead sheet was added for secondary protecting of non-targeting areas.

For pelvic side wall, 6~8 cm sized elliptical applicators with 30° beveled was most commonly used in our experience. Details of applicators will be presented in other publication.

4. IORT Dose, Dose Distribution and Electron Energy

Single dose of 1200 cGy with 9 MeV electron energy at 90% isodose line was delivered routinely unless special parameter is required. The depth from the surface of 90% of isodose line was 2.0 cm ~2.3 cm which is satisfied for possible micro- or macro-residual cancer. Surface and depth dose distribution were illustrated in Fig. 3.

5. External Irradiation

Postoperative external irradiation is started within 4 weeks of operation unless wound problem or other unexpected stuations. AP and PA or 4 field technique was used for whole pelvis with our 10 MV Linac (NELAC-1018D) with include fifth lumbar vertebra superiorly, 1.5 cm from pelvic brims laterally, and lower margin of obturator foramen (low anterioir resection) or perineum (abdomino-perineal resection) inferiorly. Total dose of 4500 cGy for whole pelvis is routine dose, with 180 cGy per fraction, five times per week regimen and 5040 cGy was maximum planned dose for grossly residual tissue.

Preoperative irradiation is also planned for tethered rectal cancer. Dose and treatment field is similar to postoperative irradiation.

6. Chemotherapy

Various dose and route of administration of 5-FU and Leucovorin is programmed the intent of reducing distant metastasis and improving survival, depend on the patient's disease and general condition. Most chemotherapy started from 7 days after completion of radiation therapy for avoiding enhancement of possible toxicity and unwanted interruption of the therapy.

7. Follow up of the Patients

All patients were followed up regularly on monthly bases. CEA is routinely checked for monitoring the possible recurrence or metastasys. Various other laboratory tests and x-ray examinations, if necessary, were ordered.

RESULTS

Since May 30th, 1991, we performed only 6 cases of IORT in colorectal cancer. Even though we cannot draw any result for local control or survival because of short follow up periods, the outcome is encouraging.

Mean operation time was about 4 hours and the time delay for IORT was only 30 minutes. No immediate operative morbidity or mortality was noted so far, in spite of B-3 or C-3 stages of the patients. The result of complications will be published within 2 years.

DISCUSSION

Colorectal cancer is the fourth most frequent malignant tumor in male and female in Korea and the incidence is approximately 6% of all primary malignant tumors[2]. At the time of operation, about 25% of the patients with colorectal cancer have distant metastases, 40% of patients had localized tumor in bowel wall and 35% has localized but spread to the regional lymphatics[17]. The proportion of the distribution has remained constantly for last decades and this data suggested that improving survival may be achieved by aggressive local treatment which consist of 75% of tumors at operation.

Surgery is the mainstay of the treatment for colorectal cancer, but the possibility always exists that microscopic lesions will be left behind even after agressive curative radical operations. Reported local recurrence was various from 40% to 92%[18] in case of nodal involvement even after curative resection. The fate of local recurrence is ominous, because more than 90% of the patients with local failure expired shortly[17] and the five year survival is less than 5%[4~6] even though massive combination theapy including surgery, radiotherapy, and chemotherapy.

Pre or post-operative radiotherapy in the range of 4000~5500 cGy have been tried for reducing local failure but still 35~45% of local failure were reported[12] and no influence on the overall survival could be detected although a little decrease of local failure[4].

Immunotherapy has also tried but the local recurrence was reported as many as 90%[14] by this modality alone. Various regimens of chemotherapy have been developed but no significant improve-

ment of survival could be achieved.

Intraoperative radiotherapy (IORT) with or without external irradiation have been advocated for reducing local failure and improving survival. Principle of IORT is the delivery of large single doses of electron beam irradiation during sugery[13]. The benefits of IORT are 1) direct visualization of the target lesion, 2) accurate determination of the target volume, 3) excluding potentially dose limiting normal tissue from the field, 4) possible delivery of high effective doses. These may permit improving local control so that further improving of survival is possible with lesser complications, therefore, increased therapeutic radiation could be obtained.

Even though such a good rationale, Minsky et al[10] reported approximately 44% of local failure by IORT alone, although Abe and Takahashi[19] reported good results, Many institutions use IORT as a boost for surgery plus pre or postoperative irradiation[11~14]. Tepper et al[12] reported 92% of 3 year survival by the treatment of IORT (1000~2000 cGy) plus preoperative irradiation (4500~5040 cGy) and only 5% of the local recurrence although all their patients were unresectable or recurrent tumors.

This data suggested us the possibility of successful local control and improving survival could be achieved by these modalities. Sindelar et al[13] and Gunderson et al[14] reported 25~59% of long term survival which were treatmendous improvement, compare to previous result (5%)[14] by conventional treatment. They also concluded that other modalities including hyperthermia, radiosensitizer and combination chemotherapy may improve more survival.

We performed total 6 cases of IORT for the patients with locally advanced colorectal cancers since last May 30th, 1991. Our treatment program enforced chemotherapy to IORT plus are or postoperative irradiation for reducing distant metastasis, respectively. We also used the pelvic reconstruction with mesh which may decrease the small bowel injury by external irradiation. Therefore we expect that our protocol can achieve better local control and survival and aoso reducing small bowel injury.

Shaw et al[20] reported that the most common complication after IORT are neuropathy and ureteral obstruction. They emphasized that nerve damage is never possible to be avoid and the limited IORT dose for preventing neuropathy is 1000~1250 cGy. Therefore we selected 1200 cGy at 90% isodose line as a IORT dose so that neuropathy is not the serious problem to our protocol.

All our patients were instructed to visit our department regularly on monthly bases for check CEA and other necessary tests. There were various controvery about the sensitivity and specificity of CEA. Martin et al[21] insisted that monthly check up were very helpful for detecting 25~50% of recurrent cancer and 95% of liver metastasis. We expect that monthly CEA check will be helpful for detecting early recurrence and make the next plan for further treatment.

We performed only 6 cases of IORT so far. Although we cannot draw any definite conclusion from our data, we hope that our protocol can contribute for increasing local control and survival in locally advanced colorectal cancer treatment. We also expect that our experience may helpful for other institutions which are preparing IORT in Korea.

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= 국문초록 =

대장-직장암의 수술중 방사선 치료

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김명세 · 김성규 · 김재황* · 권굉보* · 김흥대**

대장-직장암은 한국에서 남녀 모두 4위의 비교적 높은 빈도를 보이고 있으며 점점 증가되는 추세에 있다. 근치적 수술요법이 주 치료방법으로 사용되어 왔으나 그 생존율은 20~50%에 불과하다. 국소재발은 특히 직장암에서 가장 흔한 실패의 원인으로서 근치적 복합요법의 발달에도 불구하고 40~92%의 높은 국소재발율이 보고되고 있어 생존율를 높이고 생존의 질을 높이기 위하여는 국소재발을 줄이는 노력이 필수적이다.

수술중 방사선 치료는 수술중에 원하는 부위에만 다량의 방사선을 한번에 조사하는 방법으로 최근 보고에서 국소재발율을 5%까지 줄일 수 있었다고 보고되고 있다. 영남대학병원 치료방사선과에서는 국내에서는 처음으로 91년 5월 30일 직장암 환자에 수술중 방사선 치료를 실시한 후 현재까지 6명의 대장 직장암 환자에 수술중 방사선 치료를 실시하였기에 환자선택, 치료선량, 선량분포, 수술 및 방사선치료과정등을 보고하고저 한다.